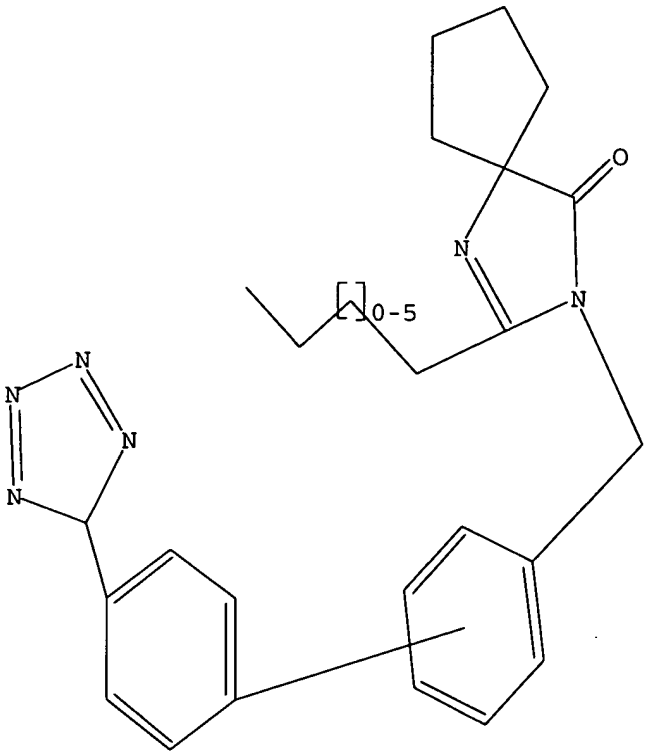

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -      5 TO ITERATE

100.0% PROCESSED       5 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            5 TO      234
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

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FULL SCREEN SEARCH COMPLETED -    157 TO ITERATE

100.0% PROCESSED     157 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

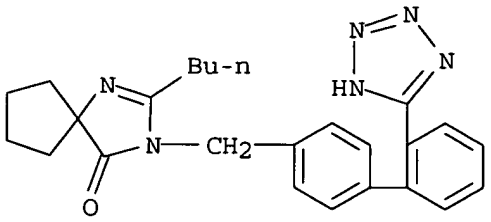
L3            0 SEA SSS FUL L1

=> s irbesartan/cn
L4            1 IRBESARTAN/CN
```

5/02/05

=> d

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 138402-11-6 REGISTRY
ED Entered STN: 17 Jan 1992
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Butyl-3-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one
CN Aprovel
CN Avapro
CN BMS 186295
CN **Irbesartan**
CN Karvea
CN SR 47436
FS 3D CONCORD
MF C25 H28 N6 O
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

610 REFERENCES IN FILE CA (1907 TO DATE)
12 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
611 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	168.20	168.41

FILE 'CAPLUS' ENTERED AT 10:54:41 ON 02 MAY 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

10759906

5/02/05

FILE COVERS 1907 - 2 May 2005 VOL 142 ISS 19
FILE LAST UPDATED: 1 May 2005 (20050501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l4
L5 611 L4

=> s l5/p
FIELD CODES CANNOT BE CHANGED HERE
You may have tried to apply a field code to a term that already has a field code. You can only add a field code to a term that has no field code appended to it.

=> s l5p
L6 4 L5P

=> d abs fbib hitstr 1-4

L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
AB We present a theory of the linear viscoelasticity of dilute solns. of freely draining, inextensible, semiflexible rods. The theory is developed expanding the polymer contour about a rigid rod reference state, in a manner that respects the inextensibility of the chain, and is asymptotically exact in the rodlike limit where the polymer length L is much less than its persistence length Lp. In this limit, the relaxation modulus G(t) exhibits three time regimes: at very early times, less than a time τ.dblvert. ∝ L8/ **L5p** required for the end-to-end length of a chain to relax significantly after a deformation, the average tension induced in each chain and G(t) both decay as t-3/4. Over a broad range of intermediate times, τ.dblvert. « t « τ⊥, where τ⊥ ∝ L4/Lp is the longest relaxation time for the transverse bending modes, the end-to-end length decays as t-1/4, while the residual tension required to drive this relaxation and G(t) both decay as t-5/4. As later times, the stress is dominated by an entropic orientational stress, giving G(t) ∝ e-t/τrod, where τrod ∝ L3 is a rotational diffusion time, as for rigid rods. Predictions for G(t) and G*(ω) are in excellent agreement with the results of Brownian dynamics simulations of discretized free draining semiflexible rods for lengths up to L = Lp, and with linear viscoelastic data for dilute solns. of poly(γ-benzyl-L-glutamate) with L .apprx. Lp.
AN 2002:663452 CAPLUS

DN 138:14261
TI Theory of linear viscoelasticity of semiflexible rods in dilute solution
AU Shankar, V.; Pasquali, Matteo; Morse, David C.
CS Department of Chemical Engineering and Materials Science, University of Minnesota, Minneapolis, MN, 421, USA
SO Journal of Rheology (New York, NY, United States) (2002), 46(5), 1111-1154
CODEN: JORHD2; ISSN: 0148-6055
PB American Institute of Physics
DT Journal
LA English
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
AB An iron(II) porphyrin/1-methylimidazole (Im) complex, covalently encapsulated within a large aryl ether dendrimer cage ((Im)2(**L5P**)FeII), shows reversible dioxygen-binding activity, in which the dioxygen adduct ((Im)(**L5P**)FeIIO2) survives over a period of months even in the presence of water. (Im)(**L5P**)FeIIO2 was highly reluctant to undergo carbonylation upon exposure to a carbon monoxide atmospheric, where the half-life of (Im)(**L5P**)FeIIO2 was as long as 50 h.
AN 1997:688750 CAPLUS
DN 128:11208
TI Dendrimer-encapsulated iron porphyrin as a novel hemoprotein mimic for dioxygen binding
AU Jiang, Dong-Lin; Aida, Takuzo
CS Dep. Chem. Biotechnol., Grad. Sch. Eng., Univ. Tokyo, Tokyo, 113, Japan
SO Journal of Macromolecular Science, Pure and Applied Chemistry (1997), A34(10), 2047-2055
CODEN: JSPCE6; ISSN: 1060-1325
PB Dekker
DT Journal
LA English
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
AB Iron porphyrins having aryl ether dendrimer units ((LnP)Fe, n; number of the aromatic layers = 1 - 5) were synthesized, and their dioxygen-binding activities were investigated. A higher generation dendritic iron porphyrin ((**L5P**)Fe), in the presence of 1-methylimidazole, showed reversible dioxygen-binding activity even in wet solvents, and survived for several months without any sign of irreversible oxidation Of further interest to note is that the dioxygen adduct within the large dendrimer framework also showed a high durability to carbonylation in carbon monoxide atmospheric, indicating that the large and tightly-packed dendrimer framework serves as a barrier for water and even gaseous small mols.
AN 1997:488945 CAPLUS
TI Dendrimer porphyrins for biomimetic applications
AU Jiang, Dong-Lin; Aida, Takuzo
CS Graduate School Engineering, University Tokyo, Tokyo, 113, Japan
SO Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (1997), PMSE-153 Publisher: American Chemical Society, Washington, D. C.
CODEN: 64RNAO
DT Conference; Meeting Abstract
LA English

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
AB Metalloporphyrins play important roles in biol. electron transfer (ET) reactions. We have synthesized the dendrimer porphyrin as a new class of photofunctional dendrimer, in which a porphyrin is encapsulated by an aryl ether dendrimer framework (LnPH2 or (LnP)Met, n [number of the aromatic layers] = 1 Å 5). Solvatochromic profiles of the (LnP)Zn family and their coordination profiles with dendrimer imidazoles showed that the encapsulation is almost accomplished for (L4P)Zn and (**L5P**)Zn (.apprx.5 nm in diameter). NMR T1 measurements indicated an egg-like structural resemblance to L4P and **L5P**, where the fluid interior is encapsulated by a stiff exterior shell. For investigating the ET events, we synthesized a water-soluble dendrimer zinc porphyrin having neg.- or pos.-charged exterior surface ((32(-)L4P)Zn or ((32(+)L4P)Zn). Upon mixing of (32(-)L4P)Zn with a pos.-charged acceptor, a spatially separated donor-acceptor assembly was formed, where a long-range ET through the dendrimer framework occurred upon photoexcitation of the interior (P)Zn unit.
AN 1997:488832 CAPLUS
TI Dendrimer porphyrins for photochemical applications
AU Aida, Takuzo
CS Graduate School Engineering, University Tokyo, Tokyo, 113, Japan
SO Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (1997), PMSE-039 Publisher: American Chemical Society, Washington, D. C.
CODEN: 64RNAO
DT Conference; Meeting Abstract
LA English

=> file casreact

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	13.39	181.80

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.92	-2.92

FILE 'CASREACT' ENTERED AT 10:56:00 ON 02 MAY 2005

FILE CONTENT:1840 - 1 May 2005 VOL 142 ISS 18

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* CASREACT now has more than 9.2 million reactions *
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Some CASREACT records are derived from the ZIC/VINITI database (1974-1991) provided by InfoChem, INPI data prior to 1986, and Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d his

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     FILE 'REGISTRY' ENTERED AT 10:53:44 ON 02 MAY 2005
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L3           0 S L1 FUL
L4           1 S IRBESARTAN/CN

     FILE 'CAPLUS' ENTERED AT 10:54:41 ON 02 MAY 2005
L5         611 S L4
L6           4 S L5P

     FILE 'CASREACT' ENTERED AT 10:56:00 ON 02 MAY 2005

=> s l4
L7           5 L4

=> d all 1-5


L7   ANSWER 1 OF 5  CASREACT  COPYRIGHT 2005 ACS on STN
AN   141:225515  CASREACT
TI   Synthesis of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-
     yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one
IN   Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia;
     Dolitzky, Ben-zion
PA   Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa,
     Inc.
SO   PCT Int. Appl., 27 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C07D403-10
CC   28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
     Section cross-reference(s): 1
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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             CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES,
             ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,
             IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC,
             LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX,
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             MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
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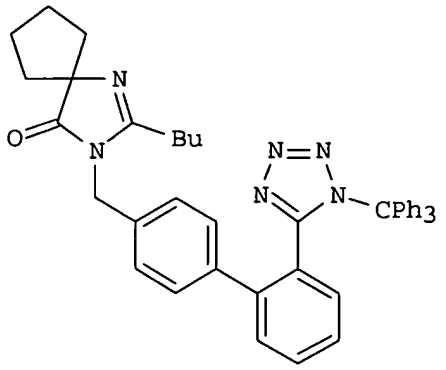

I

AB Provided are 5 methods of making 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-ene-4-one (I), e.g. comprising the steps of: (a) reacting 1-(N'-pentanoylamino)cyclopentanecarboxylic acid amide with 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole in the presence of an inorg. base, a solvent and a phase transfer catalyst; (b) cooling the mixture; (c) adding water to the mixture whereby two phases are obtained; (d) separating the two phases obtained; and (e) recovering the compound I. The compds. I can be converted to irbesartan which is a known angiotensin II receptor antagonist (blocker).

ST butyltrityltetrazolylbiphenylylmethyldiazaspirolenone prepn intermediate irbesartan

IT Ethers, uses
RL: NUU (Other use, unclassified); USES (Uses)
(aliphatic, solvent; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT Phosphonium compounds
Quaternary ammonium compounds, uses
RL: CAT (Catalyst use); USES (Uses)
(catalysts for cyclocondensation of (pentanoylamino)cyclopentanecarboxamide with (bromomethylbiphenylyl)tetrazole; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT Cyclocondensation reaction
(cyclocondensation of (pentanoylamino)cyclopentanecarboxamide with (bromomethylbiphenylyl)tetrazole; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT Acetals
RL: NUU (Other use, unclassified); USES (Uses)
(formals, solvent; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT Ethers, uses
RL: NUU (Other use, unclassified); USES (Uses)
(glymes, solvent; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-

tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT Acids, uses
RL: CAT (Catalyst use); USES (Uses)
(inorg., catalysts for imidation of valerimidate ester with (aminomethylbiphenylyl)tetrazole; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT Phase transfer catalysts
(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT Cyclocondensation reaction catalysts
(phase transfer catalysts, cyclocondensation of (pentanoylamino)cyclopentanecarboxamide with (bromomethylbiphenylyl)tetrazole; preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT Aromatic hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 32503-27-8, Tetrabutylammonium hydrogen sulfate
RL: CAT (Catalyst use); USES (Uses)
(catalysts for cyclocondensation of (pentanoylamino)cyclopentanecarboxamide with (bromomethylbiphenylyl)tetrazole; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 64-18-6, Formic acid, uses 64-19-7, Acetic acid, uses 7647-01-0, Hydrochloric acid, uses 10035-10-6, Hydrobromic acid, uses
RL: CAT (Catalyst use); USES (Uses)
(catalysts for imidation of valerimidate ester with (aminomethylbiphenylyl)tetrazole; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 57246-71-6, Methyl valerimidate
RL: RCT (Reactant); RACT (Reactant or reagent)
(catalysts for imidation of valerimidate ester with (aminomethylbiphenylyl)tetrazole; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 76-05-1, Trifluoroacetic acid, uses
RL: CAT (Catalyst use); USES (Uses)
(catalysts for imidation of valerimidate ester with 5-(4'-aminomethylbiphenyl-2-yl)tetrazole; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 999-09-7, Ethyl valerimidate 745814-12-4, Propyl valerimidate 745814-13-5, Butyl valerimidate 745814-14-6, Benzyl valerimidate 745814-15-7, Pentyl valerimidate
RL: RCT (Reactant); RACT (Reactant or reagent)
(imidation of valerimidate ester with (aminomethylbiphenylyl)tetrazole; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 638-29-9, Valeroyl chloride 1664-35-3, 1-Aminocyclopentanecarboxylic acid ethyl ester 17193-28-1, 1-Aminocyclopentanecarboxamide 134603-82-0, 2-(1-Trityl-1H-tetrazol-5-yl)-4'-(aminomethyl)-1,1'-biphenyl 745814-07-7, Ethyl valerimidate methanesulfonate 745814-11-3, 1-(Pentanoylamino)cyclopentanecarboxylic acid ethyl ester
RL: RCT (Reactant); RACT (Reactant or reagent)

(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 124750-51-2P, 5-(4'-Bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole 177219-40-8P, 1-(Pentanoylamino)cyclopentanecarboxamide 439904-79-7P, N-[[2'-(1-Trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pentanamide 745814-08-8P 745814-10-2P, 1-[(1-Ethoxypentylidene)amino]cyclopentanecarboxylic acid ethyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 79-37-8, Oxalyl chloride 108-48-5, 2,6-Lutidine 144-55-8, Sodium bicarbonate, reactions 584-08-7, Potassium carbonate 1310-58-3, Potassium hydroxide, reactions 1310-73-2, Sodium hydroxide, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 745814-09-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 138402-11-6P, Irbesartan
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

IT 68-12-2, N,N-Dimethylformamide, uses 71-43-2, Benzene, uses 95-47-6, o-Xylene, uses 108-38-3, m-Xylene, uses 108-88-3, Toluene, uses 109-99-9, Tetrahydrofuran, uses 110-54-3, Hexane, uses 110-71-4, 1,2-Dimethoxyethane 119-64-2, Tetralin 127-19-5, N,N-Dimethylacetamide 462-95-3, Diethoxymethane 1634-04-4, Methyl tert-butyl ether
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

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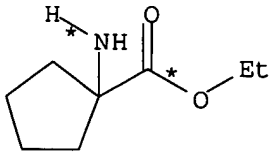

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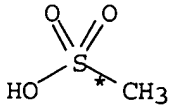

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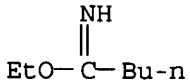

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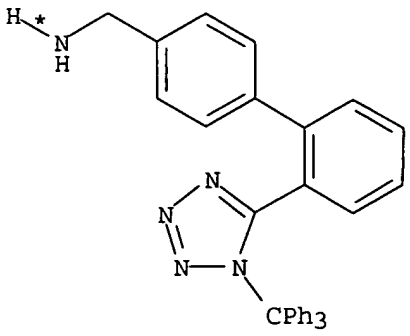

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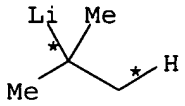

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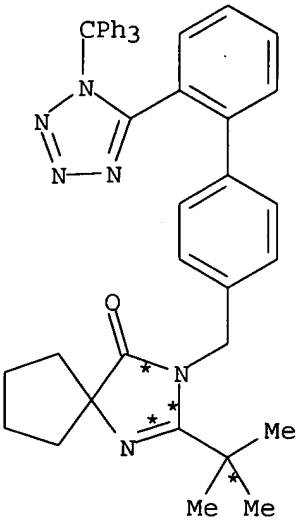


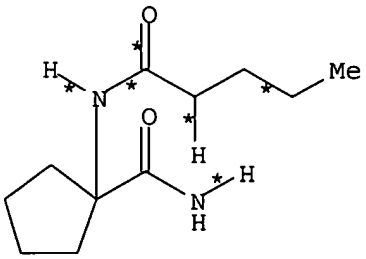
E
YIELD 50%

RX(1) RCT A 1664-35-3, B 745814-07-7

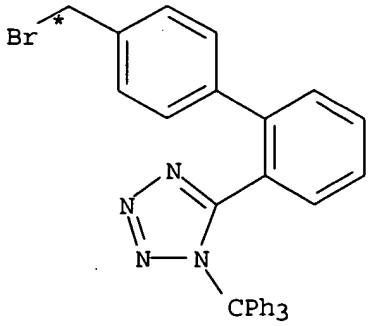
STAGE(1)
SOL 108-88-3 PhMe

STAGE(2)
RCT C 134603-82-0, D 594-19-4
CAT 64-19-7 AcOH
PRO E 745814-09-9

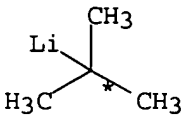
RX(2) OF 8 ...H + I + 2 D ===> E



H

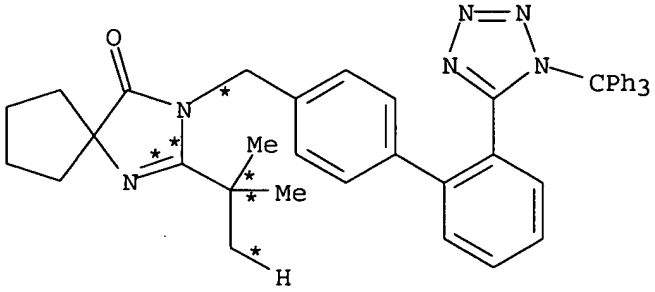


I



2 D

(2) →



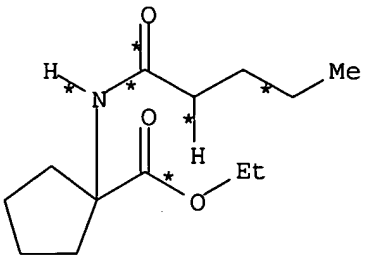
E
YIELD 86%

RX(2) RCT H 177219-40-8, I 124750-51-2

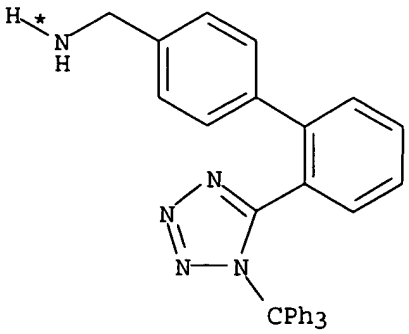
STAGE(1)
RGT J 1310-58-3 KOH
CAT 32503-27-8 Bu4N.HSO4
SOL 7732-18-5 Water

STAGE(2)
RCT D 594-19-4
SOL 7732-18-5 Water
PRO E 745814-09-9

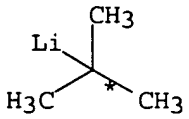
RX(3) OF 8 M + C + 2 D ===> E



M

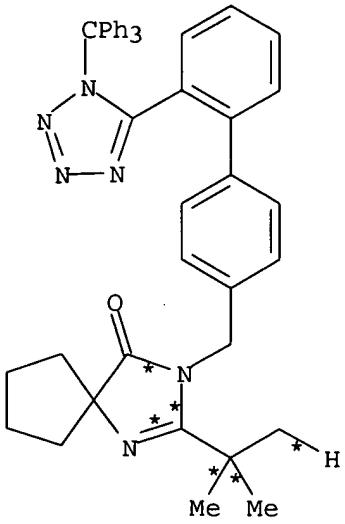


C



2 D

(3) →



E
YIELD 30%

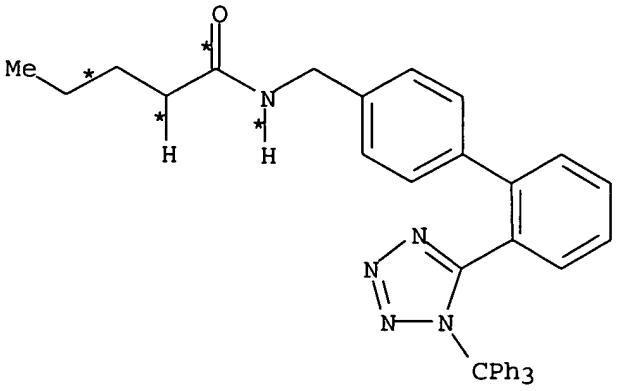
RX(3) RCT M 745814-11-3

STAGE(1)
RGT N 108-48-5 2,6-Lutidine, O 79-37-8 (COCl)2
SOL 108-88-3 PhMe

STAGE(2)
RCT C 134603-82-0, D 594-19-4
SOL 108-88-3 PhMe
PRO E 745814-09-9

5/02/05

RX(4) OF 8 P + A + 2 D ===> E



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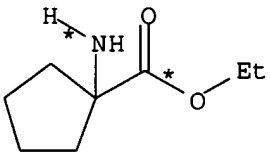
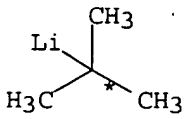
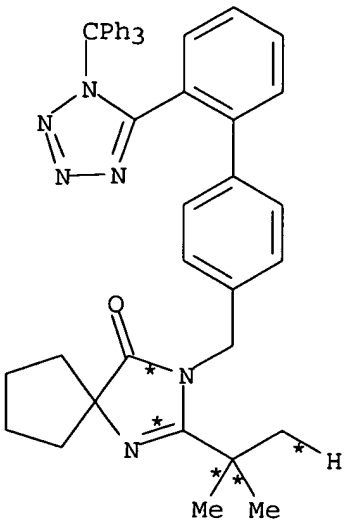


A



2 D

(4)



E
YIELD 25%

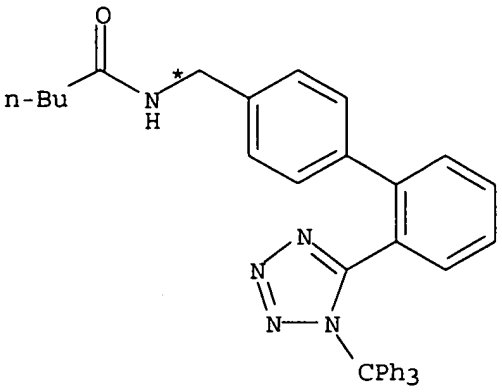
RX(4) RCT P 439904-79-7

STAGE(1)
RGT N 108-48-5 2,6-Lutidine, O 79-37-8 (COCl)2
SOL 108-88-3 PhMe

STAGE(2)
RCT A 1664-35-3, D 594-19-4
SOL 108-88-3 PhMe
PRO E 745814-09-9

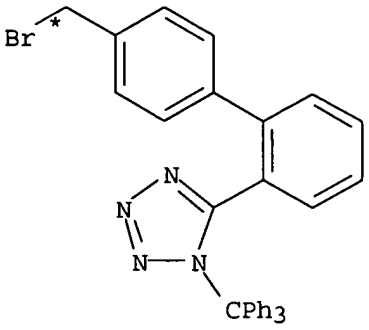
5/02/05

RX(5) OF 8 P ===> I...



P

(5)



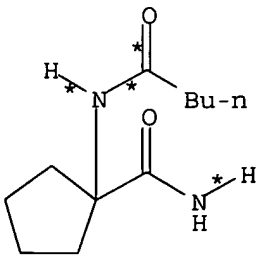
I
YIELD 87%

RX(5) RCT P 439904-79-7

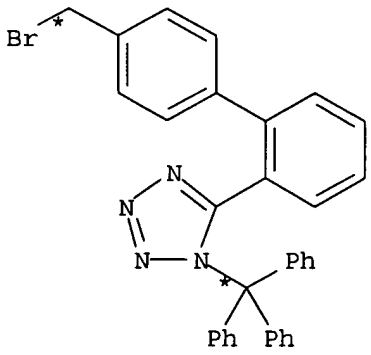
STAGE(1)
RGT Q 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2)
RGT R 638-29-9 Pentanoyl chloride, S 17193-28-1
Cyclopentanecarboxamide, 1-amino-
SOL 109-99-9 THF
PRO I 124750-51-2

RX(6) OF 8 ...H + I ===> **U**

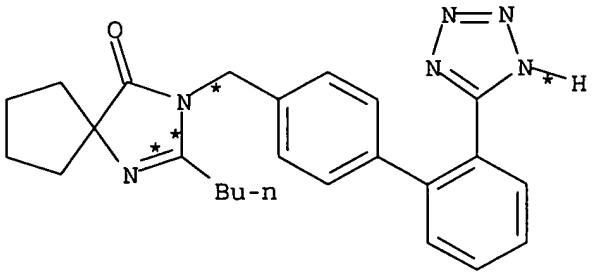


H



I

(6)



U
YIELD 85%

RX(6) RCT H 177219-40-8, I 124750-51-2

STAGE(1)
RGT J 1310-58-3 KOH
CAT 32503-27-8 Bu4N.HSO4
SOL 7732-18-5 Water

STAGE(2)
SOL 7732-18-5 Water

STAGE(3)
RGT V 7647-01-0 HCl
SOL 67-64-1 Me2CO, 7732-18-5 Water

STAGE(4)
RGT J 1310-58-3 KOH
SOL 7732-18-5 Water
PRO U **138402-11-6**

L7 ANSWER 2 OF 5 CASREACT COPYRIGHT 2005 ACS on STN
AN 141:157121 CASREACT
TI Synthesis of irbesartan
IN Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-zion
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D403-10
ICS C07D235-02; C07D257-00; C07D235-00
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004065383	A2	20040805	WO 2004-US1135	20040116
WO 2004065383	A3	20041216		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG,

priority

ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU,
ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ,
KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN,
MW, MX, MX, MZ

US 2004192713 A1 20040930 US 2004-759906 20040116
EP 1509517 A2 20050302 EP 2004-702955 20040116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRAI US 2003-440997P 20030116
WO 2004-US1135 20040116

AB Provided are a method of making irbesartan via a Suzuki coupling reaction and a novel intermediate, 2-butyl-3-(4'-bromobenzyl)-1,3-diazaspiro[4.4]non-1-ene-4-one, for such process. The novel process includes the step of reacting such intermediate with a protected tetrazolylphenylboronic acid.

ST irbesartan prepn; bromobenzyldiazaspirononenone Suzuki coupling tetrazolylphenylboronic acid

IT Suzuki coupling reaction
(synthesis of irbesartan via Suzuki coupling reaction of bromobenzyldiazaspirononenone with tetrazolylphenylboronic acid)

IT 603-35-0, Triphenylphosphine, uses 3375-31-3, Palladium diacetate
RL: CAT (Catalyst use); USES (Uses)
(synthesis of irbesartan)

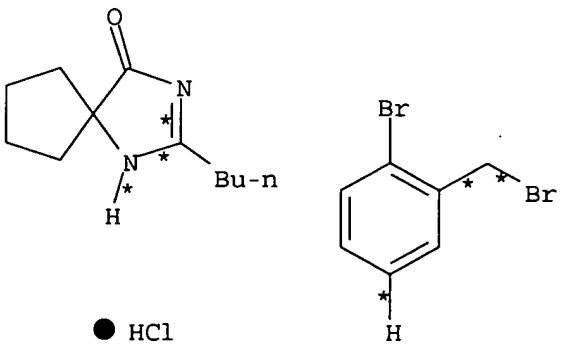
IT 138402-11-6P, Irbesartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(synthesis of irbesartan)

IT 76-83-5, Trityl chloride 3433-80-5, o-Bromobenzyl bromide 5419-55-6, Triisopropyl borate 18039-42-4 151257-01-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of irbesartan)

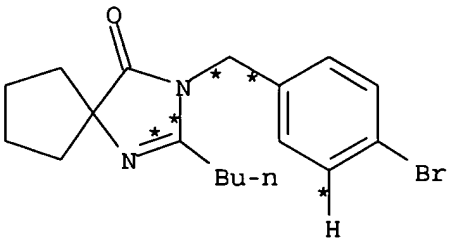
IT 138402-10-5P 144873-97-2P 154750-11-5P 731851-41-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of irbesartan)

IT 1310-58-3, Potassium hydroxide, reactions 32503-27-8, Tetrabutylammonium hydrogen sulfate
RL: RGT (Reagent); RACT (Reactant or reagent)
(synthesis of irbesartan)

RX(1) OF 17 A + B ===> C...



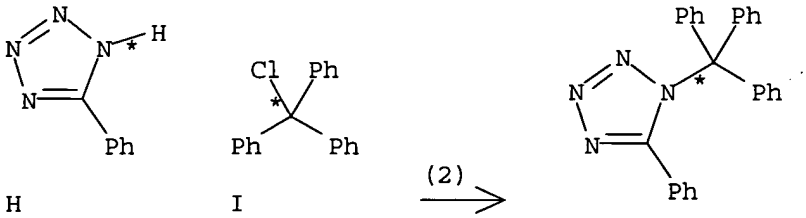
A B (1) →



C
YIELD 94%

RX(1) RCT A 151257-01-1, B 3433-80-5
RGT D 1310-58-3 KOH
PRO C 731851-41-5
CAT 32503-27-8 Bu4N.HSO4
SOL 108-88-3 PhMe, 7732-18-5 Water

RX(2) OF 17 H + I ===> J...

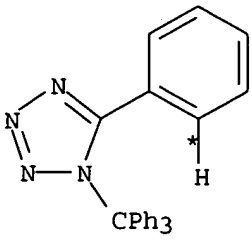


H I J

J
YIELD 94%

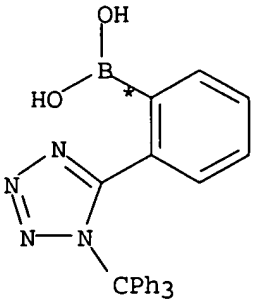
RX(2) RCT H 18039-42-4, I 76-83-5
RGT K 121-44-8 Et3N
PRO J 154750-11-5
SOL 109-99-9 THF

RX(3) OF 17 ...J ===> M...



J

(3)



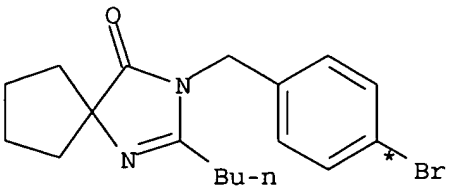
M
YIELD 92%

RX(3) RCT J 154750-11-5

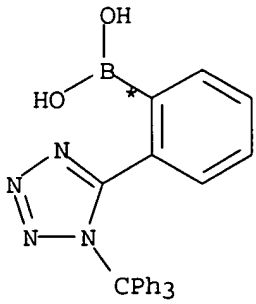
STAGE(1)
RGT N 109-72-8 BuLi
SOL 109-99-9 THF

STAGE(2)
RGT O 5419-55-6 Boric acid (H3BO3), tris(1-methylethyl) ester
PRO M 144873-97-2

RX(4) OF 17 ...C + M ===> P...

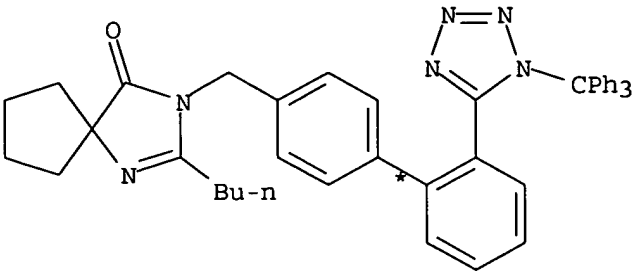


C



M

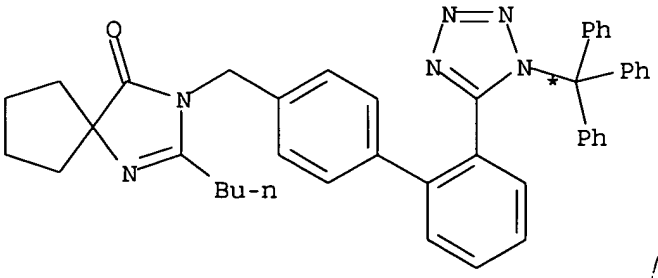
(4)



P
YIELD 90%

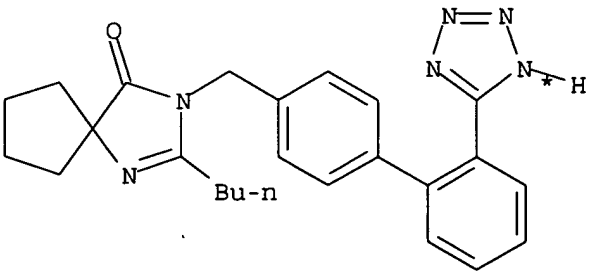
RX(4) RCT C 731851-41-5, M 144873-97-2
RGT Q 584-08-7 K2CO3
PRO P 138402-10-5
CAT 3375-31-3 Pd(OAc)2, 603-35-0 PPh3
SOL 110-71-4 (CH2OMe)2, 109-99-9 THF

RX(5) OF 17 ...P ===> **U**



P

(5)



U

RX(5) RCT P 138402-10-5

RGT V 7647-01-0 HCl
PRO U **138402-11-6**
SOL 7732-18-5 Water, 67-64-1 Me2CO

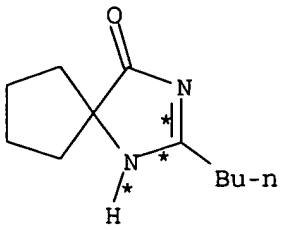
L7 ANSWER 3 OF 5 CASREACT COPYRIGHT 2005 ACS on STN
AN 140:111420 CASREACT
TI Synthesis of irbesartan
IN Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-Zion; Shapiro, Eugeny; Yahalomi, Bonit
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D403-00
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004007482	A2	20040122	WO 2003-US22479	20030716
	WO 2004007482	A3	20040527		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

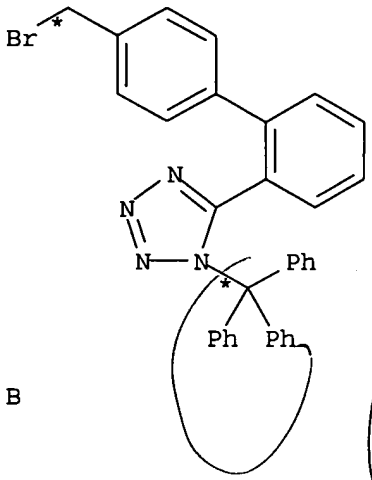
PRAI US 2002-396424P 20020716
US 2002-402490P 20020809
AB Irbesartan is prepared by reaction of 2-butyl-1,3-diaza-spiro[4.4]non-1-ene (I) with 5-(4-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole (II) in the presence of a phase transfer catalyst. Thus, reaction of I with II in toluene in the presence of Bu4NHSO4 at 90° for 1.5 h gave, after deprotection, 84.3% irbesartan. Also provided is irbesartan having a fine particle size.
ST irbesartan prepn
IT Quaternary ammonium compounds, uses
RL: CAT (Catalyst use); USES (Uses)
(preparation of irbesartan)
IT 32503-27-8, Tetrabutylammonium hydrogen sulfate
RL: CAT (Catalyst use); USES (Uses)
(preparation of irbesartan)
IT 138402-11-6P, Irbesartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of irbesartan)
IT 124750-51-2 138402-05-8 138402-10-5 151257-01-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of irbesartan)

RX(1) OF 2 A + B ===> **C**



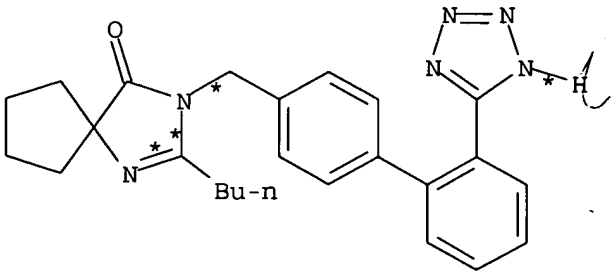
● HCl

A



B

(1)



C
YIELD 84%

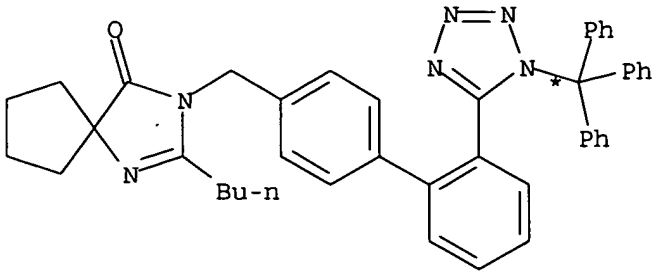
RX(1) RCT A 151257-01-1, B 124750-51-2

STAGE(1)
RGT D 1310-58-3 KOH
CAT 32503-27-8 Bu4N.HSO4
SOL 7732-18-5 Water, 108-88-3 PhMe

STAGE(2)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water, 67-64-1 Me2CO

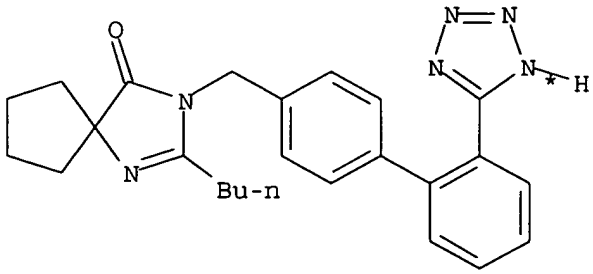
STAGE(3)
RGT D 1310-58-3 KOH
SOL 7732-18-5 Water
PRO C **138402-11-6**

RX(2) OF 2 J ===> **C**



J

(2) →



C
YIELD 93%

RX(2) RCT J 138402-10-5

STAGE(1)
RGT K 7664-93-9 H2SO4
SOL 7732-18-5 Water, 67-64-1 Me2CO

STAGE(2)
RGT D 1310-58-3 KOH
SOL 7732-18-5 Water
PRO C **138402-11-6**

L7 ANSWER 4 OF 5 CASREACT COPYRIGHT 2005 ACS on STN
AN 136:183766 CASREACT
TI Improvement on synthetic technology of irbesartan
AU Shen, Jingshan; Yan, Tiema; Li, Huijun; Li, Jianfeng; Lei, Lijun; Ji, Ruyun
CS Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SO Zhongguo Yaowu Huaxue Zazhi (2001), 11(2), 104-106
CODEN: ZYHZEF; ISSN: 1005-0108
PB Zhongguo Yaowu Huaxue Zazhi Bianjibu
DT Journal
LA Chinese
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

5/02/05

AB Two methods for synthesizing irbesartan were presented. Irbesartan was prepared from 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (I) and 4-bromomethyl-2'-cyanobiphenyl by substitution and cyclization with a good yield of 63%. It can also be obtained from I and 2-(4'-bromo-1,1'-biphenyl-2-yl)-2-triphenylmethyltetrazole through substitution and deprotection with overall yield of 85%. The structure was confirmed by 1H-NMR and MS.

ST irbesartan prepn antihypertensive

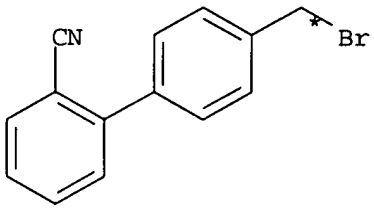
IT Antihypertensives
(synthesis of irbesartan)

IT 114772-54-2, 4-Bromomethyl-2'-cyanobiphenyl 124750-51-2 138402-05-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of irbesartan)

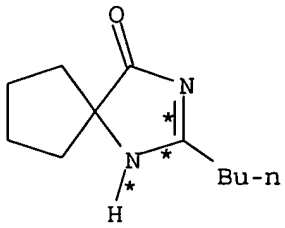
IT 138401-24-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of irbesartan)

IT 138402-11-6P, Irbesartan
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of irbesartan)

RX(1) OF 4 A + B ===> C...

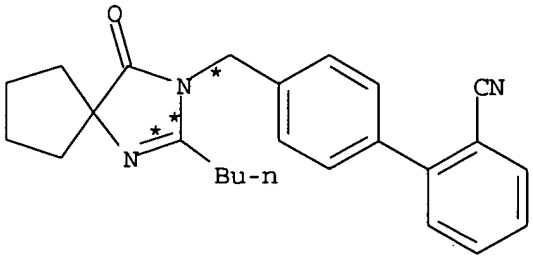


A



B

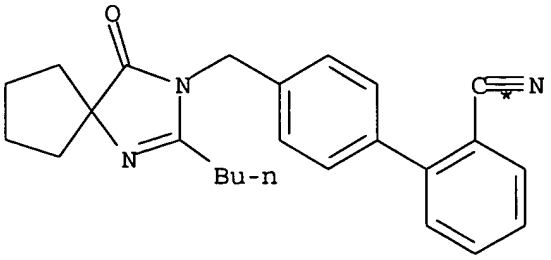
(1) →



C
YIELD 78%

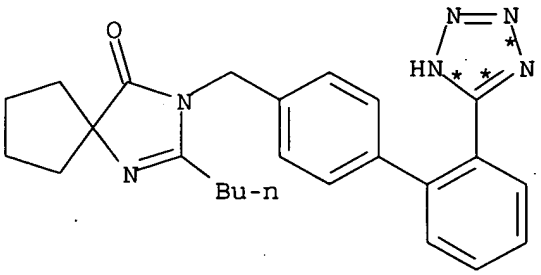
RX(1) RCT A 114772-54-2, B 138402-05-8
RGT D 7646-69-7 NaH
PRO C 138401-24-8
SOL 68-12-2 DMF

RX(2) OF 4 ...C ===> **F**



C

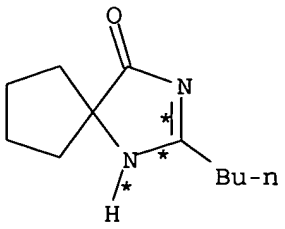
(2) →



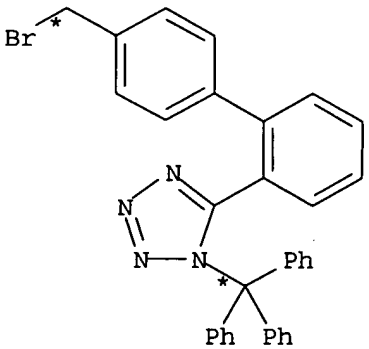
F
YIELD 81%

RX(2) RCT C 138401-24-8
RGT G 26628-22-8 NaN3, H 12125-02-9 NH4Cl
PRO F **138402-11-6**
SOL 68-12-2 DMF

RX(3) OF 4 B + I ===> **F**

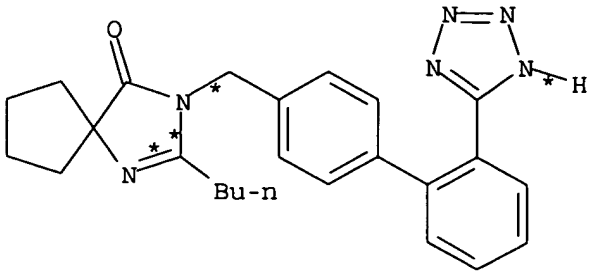


B



I

(3) →



F
YIELD 85%

RX(3) RCT B 138402-05-8, I 124750-51-2

STAGE(1)
RGT J 124-41-4 NaOMe
SOL 68-12-2 DMF

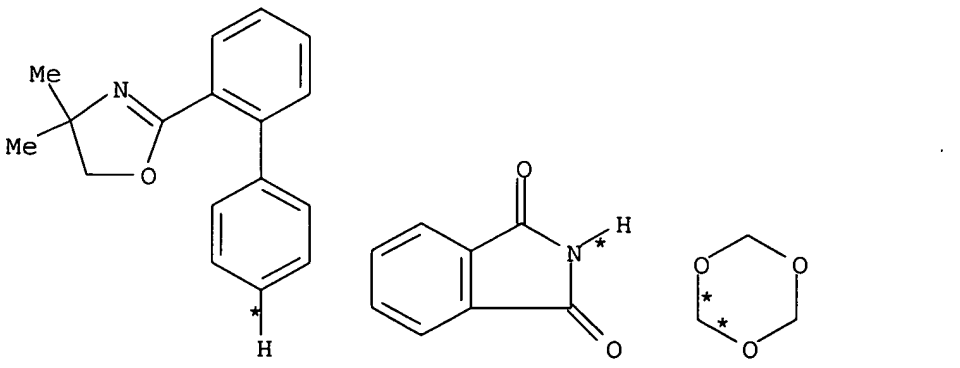
STAGE(2)
RGT K 7647-01-0 HCl
SOL 7732-18-5 Water, 109-99-9 THF
PRO F **138402-11-6**

L7 ANSWER 5 OF 5 CASREACT COPYRIGHT 2005 ACS on STN
AN 130:168359 CASREACT
TI Preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls
IN Castro, Bertrand; Dormoy, Jean-Robert; Mach, Mateusz; Makosza, Mieczyslaw; Pankowski, Jacek
PA Sanofi, Fr.
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA French
IC ICM C07D413-10
ICS C07D403-10; C07D413-10; C07D263-00; C07D209-00; C07D403-10; C07D257-00; C07D233-00; C07D403-10; C07D257-00; C07D235-00
CC 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))
FAN.CNT 1

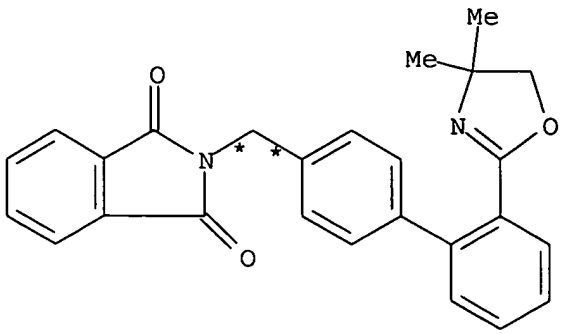
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9906398	A1	19990211	WO 1998-FR1651	19980727
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	FR 2766821	A1	19990205	FR 1997-9653	19970729
	AU 9888684	A1	19990222	AU 1998-88684	19980727

PRAI FR 1997-9653 19970729
WO 1998-FR1651 19980727
OS MARPAT 130:168359
AB 4-R1C6H4C6H4(CH2R)-4 (R = phthalimido)[I; R1 = 4(4)-(di)methyl-2-oxazolin-2-yl] were prepared as synthetic intermediates. Thus, 2-PhC6H4CO2H was cyclocondensed with Me2CH(NH2)CH2OH and the product condensed with phthalimide and trioxane to give I (R1 = 4,4-dimethyl-2-oxazolin-2-yl). The latter was used in synthesis of irbesartan a cardiovascular agent.
ST oxazolinylphthalimidomethylbiphenyl prepn
IT Aminomethylation
(preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls)
IT 57598-40-0P 133690-92-3P 138401-24-8P 138402-10-5P 147225-66-9P 220398-99-2P 220399-00-8P 220399-02-0P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls)
IT 138402-11-6P, Irbesartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls)
IT 76-83-5, Trityl chloride 85-41-6, Phthalimide 124-68-5, 2-Amino-2-methyl-1-propanol 947-84-2, [1,1'-Biphenyl]-2-carboxylic acid 6168-72-5, 2-Amino-1-propanol 138402-05-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls)
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ciba Geigy AG; EP 0475898 A 1992 CAPLUS
(2) Merck & Co Inc; FR 2182952 A 1973 CAPLUS
(3) Merck & Co Inc; WO 9220662 A 1992 CAPLUS
(4) Samant, S; J Indian Chem Soc 1979, V56(10), P1002 CAPLUS
(5) Spinale, F; US 5541209 A 1996 CAPLUS
(6) Wellcome Found; EP 0059983 A 1982 CAPLUS
(7) Wirth, J; US 3723449 A 1973 CAPLUS

RX(1) OF 31 ...A + B + C ===> D...



A B C



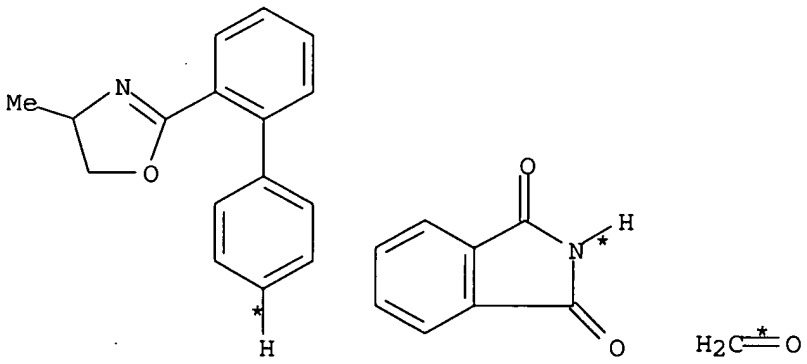
D
YIELD 80%

RX(1) RCT A 57598-40-0, B 85-41-6

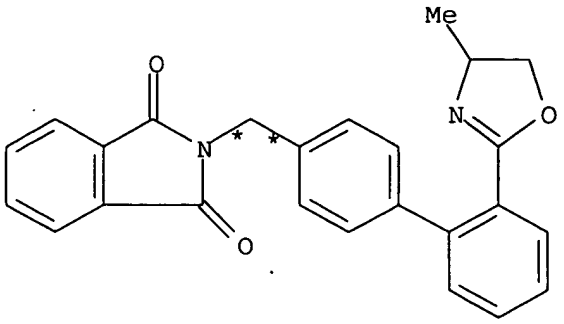
STAGE(1)
SOL 75-52-5 MeNO2

STAGE(2)
RCT C 110-88-3
RGT E 7664-93-9 H2SO4
PRO D 220399-00-8
NTE using other acids/solvents gave lower yields

RX(2) OF 31 ...G + B + H ===> I



G B H (2) →



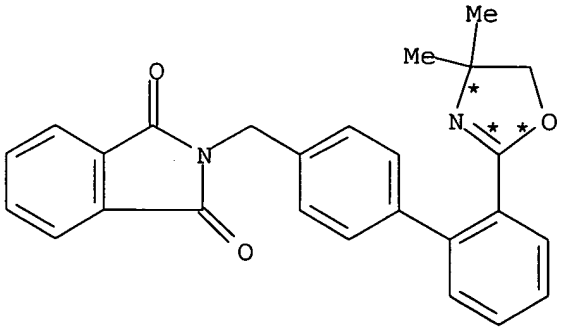
I
YIELD 72%

RX(2) RCT G 220398-99-2, B 85-41-6

STAGE(1)
SOL 75-52-5 MeNO2

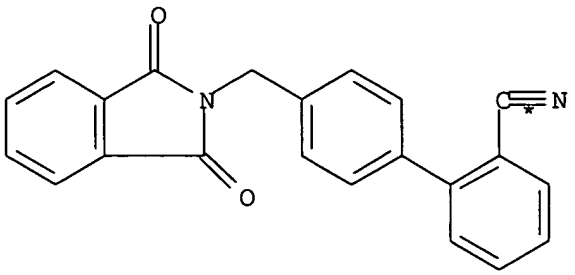
STAGE(2)
RCT H 50-00-0
RGT E 7664-93-9 H2SO4
PRO I 220399-02-0
NTE paraformaldehyde used

RX(3) OF 31 ...D ===> J...



D

(3)



J
YIELD 90%

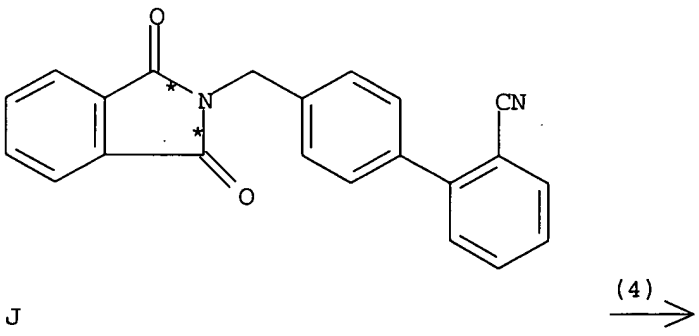
RX(3) RCT D 220399-00-8

STAGE(1)
RGT K 10025-87-3 POCl3
SOL 110-86-1 Pyridine

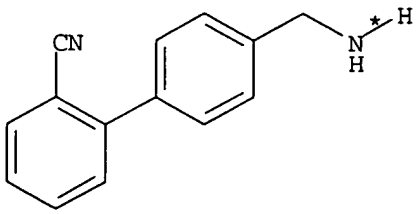
STAGE(2)
RGT L 7732-18-5 Water

STAGE(3)
RGT M 7647-01-0 HCl
SOL 7732-18-5 Water, 75-09-2 CH2Cl2
PRO J 147225-66-9

RX(4) OF 31 ...J ===> P...



J (4) →



P
YIELD 82%

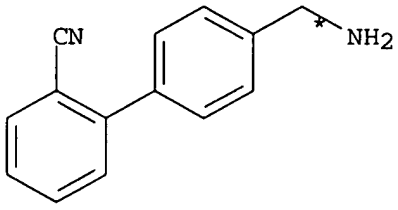
RX(4) RCT J 147225-66-9

STAGE(1)
RGT Q 302-01-2 N2H4, R 64-19-7 AcOH
SOL 109-99-9 THF, 67-63-0 Me2CHOH

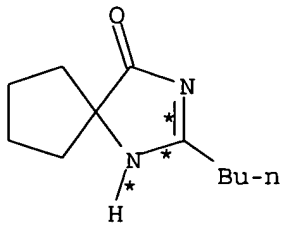
STAGE(2)
SOL 67-56-1 MeOH

STAGE(3)
RGT S 1310-73-2 NaOH
SOL 7732-18-5 Water
PRO P 133690-92-3

RX(5) OF 31 ...P + W ===> X...

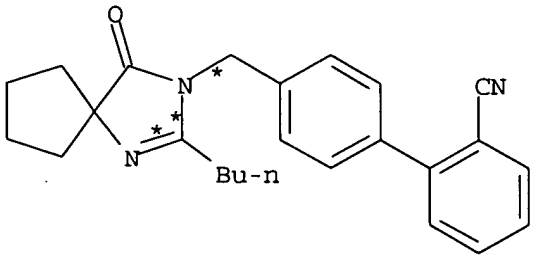


P



W

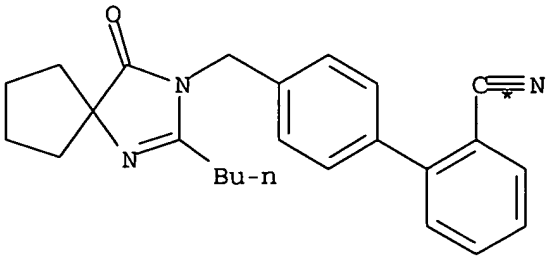
(5) ⟶



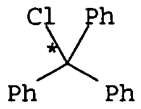
X
YIELD 65%

RX(5) RCT P 133690-92-3, W 138402-05-8
PRO X 138401-24-8
CAT 54761-04-5 Methanesulfonic acid, trifluoro-, ytterbium(3+) salt
SOL 142-96-1 Bu2O

RX(6) OF 31 ...X + AA ===> AB...

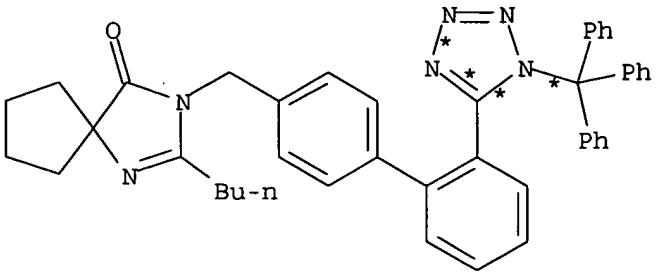


X



AA

(6) ⟶



AB

RX(6) RCT X 138401-24-8

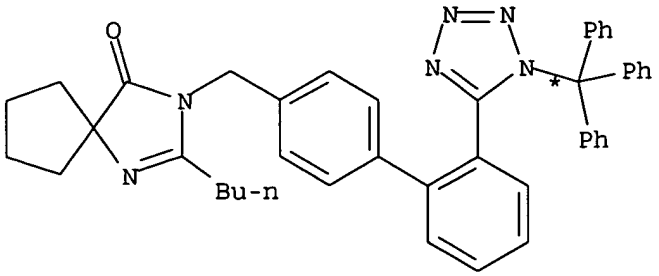
STAGE(1)
RGT AC 688-73-3 Bu3SnH
SOL 1330-20-7 Xylene

STAGE(2)
RGT S 1310-73-2 NaOH
SOL 7732-18-5 Water, 75-09-2 CH2Cl2, 109-99-9 THF

STAGE(3)
RCT AA 76-83-5

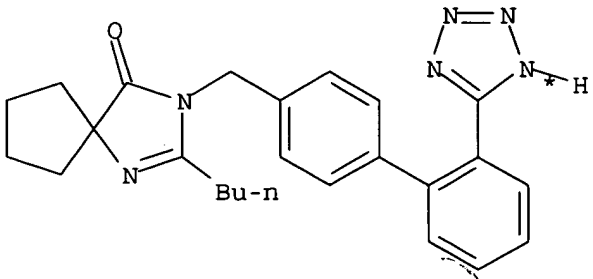
STAGE(4)
RGT L 7732-18-5 Water
SOL 141-78-6 AcOEt
PRO AB 138402-10-5

RX(7) OF 31 ...AB ===> **AF**



AB

(7)



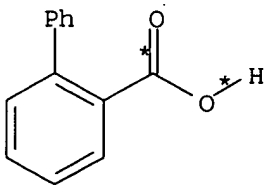
AF

RX(7) RCT AB 138402-10-5

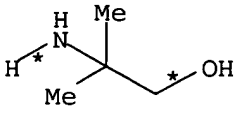
STAGE(1)
RGT M 7647-01-0 HCl
SOL 67-56-1 MeOH, 109-99-9 THF, 7732-18-5 Water

STAGE(2)
RGT S 1310-73-2 NaOH
SOL 7732-18-5 Water
PRO AF **138402-11-6**

RX(8) OF 31 AG + AH ===> A...

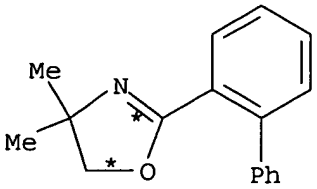


AG



AH

(8)



A
YIELD 92%

RX(8) RCT AG 947-84-2

STAGE(1)
RGT AI 79-37-8 (COCl)2
SOL 75-09-2 CH2Cl2

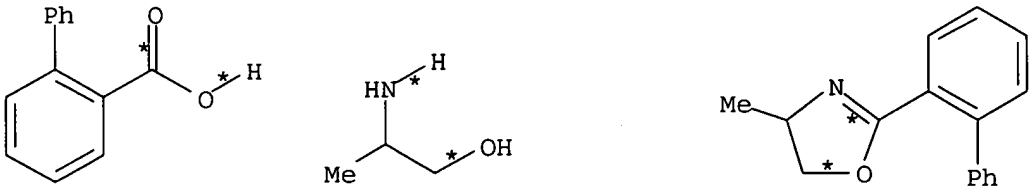
STAGE(2)
RCT AH 124-68-5
SOL 75-09-2 CH2Cl2

STAGE(3)
RGT AJ 7719-09-7 SOCl2

STAGE(4)
RGT L 7732-18-5 Water

STAGE(5)
RGT S 1310-73-2 NaOH
SOL 7732-18-5 Water
PRO A 57598-40-0

RX(9) OF 31 AG + AK ===> G...



AG AK G
YIELD 46%

RX(9) RCT AG 947-84-2

STAGE(1)
RGT AI 79-37-8 (COCl)2
SOL 75-09-2 CH2Cl2

STAGE(2)
RCT AK 6168-72-5
SOL 75-09-2 CH2Cl2

STAGE(3)
RGT AJ 7719-09-7 SOCl2

STAGE(4)
RGT L 7732-18-5 Water

STAGE(5)
RGT S 1310-73-2 NaOH
SOL 7732-18-5 Water
PRO G 220398-99-2

5/02/05

10759906